REQUEST FOR RECONSIDERATION

A. Status of the Claims

Claims 1-31 and 33-37 were pending at the time of the Action and stand rejected under 35 U.S.C. §112, first paragraph. Claims 12, 13, 14, 23, and 25 have been canceled herein without prejudice or disclaimer. The specific grounds for rejection, and applicants' response thereto, are set out in detail below. Claims 5-10 and 61-135 have been withdrawn from consideration. Claims 1-4, 11, 15-22, 24, 26-31 and 33-37 are now pending in the case and are presented for reconsideration. Support for claim amendments may be found in the specification as originally filed in the case. In particular, support can be found at least on page 5, lines 26 and 27; page 29, lines 1 to 25; and pages 32-35.

B. Election/Restriction

Claims 61-135 have been withdrawn from consideration as being patentably distinct. Applicants reserve the right to file continuing applications directed to this subject matter.

C. Oath/Declaration is not Defective

The Action states that the oath/declaration is defective for failing to provide a post office address for each inventor. Applicants draw the Examiners attention to the inventor's information section of page 2 of the Declaration and in particular the phrase in parenthesis under Post Office Address that reads: "if different from above". The inventors post office addresses are the same as the residence addresses, which is indicated by the Post Office Address box being left blank. Applicants respectfully request the withdrawal of the objection.

D. Rejections Under 35 U.S.C. §112, First Paragraph

The Action rejects claims 1-4, 11-31 and 33-37 under 35 U.S.C. §112, first paragraph as allegedly not being enabled by the specification. Applicants first note that a common thread again running through many of the rejections in the Action is that Applicants' claims are said to lack enablement for each and every embodiment that might be covered. For example, the Action states that the specification "does not reasonably provide enablement for treating *any* type of hyperproliferative disease comprising the intradermal administration of *any* type of expression construct encoding *any* tumor supressor gene." Emphasis added, Action at page 4.

Enablement must bear only a *reasonable* relationship to the scope of the claims, as described in Applicants' previous response. *In re Fisher*, 166 U.S.P.Q. 18, 24 (CCPA 1970). The applicable legal standard does *not* require that all conceivable embodiments encompassed by the claims have been demonstrated to be operable. Applying this correct standard, as explained below, the present claims are fully enabled.

i.) Claims 1-4 11-31 and 33-37 are Enabled for the Treatment of Hyperproliferative Diseases

The Action rejects claims 1-4, 11-31 and 33-37 as lacking enablement in the specification for the treatment of any and all hyperproliferative diseases. However, the scientific reasoning provided in the Action fails to rebut or dispute the working examples and guidance provided in the specification. Applicants nonetheless note that, in the interest of expediting prosecution, the claims have been amended herein and are currently directed to cancer or pre-cancerous diseases. This aspect of the 35 U.S.C. §112, first paragraph rejection is thus moot.

ii.) Claims 1-4 and 11-37 are Enabled for the Use of Adenovirus Expression Constructs for Transduction of Dendritic Cells

Applicants note that, in the interest of expedited prosecution the claims have been amended herein and are currently directed to administration of expression constructs in an adenovirus particle.

The Action alleges, generally, that achieving therapeutic levels of gene expression using currently available vectors is not enabled, although, the Action states that the use of plasmid vectors are enabled. In particular, the Action cites various articles said to challenge the ability to achieve gene expression. However, the standard of enablement involves a person who has ordinary skill in and knowledge of the art. No evidence has been provided to indicate that such a person would not be able to employ the teachings of the application, in particular, the use of an adenovirus administered intradermally, with his or her knowledge of the art and treat a human subject having or suspected of having cancer or pre-cancerous disease. Examples need not be presented for every single embodiment of this aspect of the invention. *In re Borkowski*, 164 U.S.P.Q. 624 (CCPA 1970).

An assertion that the disclosure is not commensurate with the scope of the claims must be supported by evidence or reasoning substantiating the doubts advanced. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (CCPA 1974). The Action has attempted to achieve this by the citation of numerous articles addressing gene therapy in general. As explained below, these citations fall short of what is needed to support the rejection and furthermore do not address the methods described in the present specification. Namely, priming of dendritic cells, unlike therapeutic levels of gene expression relied upon in the studies cited, need not rely on high transduction efficiency for

therapeutic efficacy due to the function of the dendritic cell in stimulating an immune response (see Kaiserian and Etchart, 1999, page 171, first column last paragraph).

Applicants also note that gene therapy encompasses a wide range of therapeutic methods and generalizations of the entire field do not necessarily apply to all methods of using genetic material as a therapy. For example, the Action relies on three references in arguing against the predictability of generating therapeutic levels of gene expression. Moreover, the particular portions of these papers relied upon by the Action evince misconceptions about the requirements of §112, first paragraph. For example, Verma *et al.* is said to report that "[t]he Achilles heel of gene therapy is gene delivery" and that "most of the approaches suffer from poor efficiency of delivery and transient expression." However, all that is required for enablement is *objective* enablement, not any particular level of efficacy. *In re Marzocchi*, 169 UPSQ 370 (CCPA 1971). The Action's reliance on the Verma article clearly relates to doubting that current vector systems *are capable of expressing therapeutic proteins in vivo*. However, the number of issued patents that bear on *this issue* indicates otherwise.

Furthermore, Marshall *et al.* and Orkin *et al.*, are cited as supporting the unpredictability of gene therapy generally and that some problems remain, mainly with regard to therapies that require replacement of defective genes, long term expression of genes and/or the transfection of large number of cells *in vivo*. However, these references also indicate that, while potentially hampered by limitations, gene therapy does in fact work. Typically, the problems expressed speak to optimization, not bare operability. This is irrelevant to enablement, which is not judged based on commercial applicability or optimization. Thus, despite the Action's attempt to "support" the rejection with these citations, it is respectfully submitted that such "evidence" and "reasoning" falls far short of that needed to establish a *prima facie* case of lack of enablement.

Furthermore, the shortcomings of such a broad category of therapies are not applicable to the specific invention presently claimed.

In addition, the Action references Hurpin *et al.* as demonstrating that the route of administration has substantial effects on the ability to generate an immune response. Although Hurpin *et al.* show a difference in ability to generate a CTL response using intradermal administration of a particular poxvirus construct and plasmid vectors, the authors do not address the differences in the vectors such as the use of different promoters or the propensity of the vectors to transfect dendritic cells. Also, the ability of the poxvirus vector was not tested for its ability to protect an animal against a tumor cell challenge. The authors state on page 210, left column, lines 15-18 that "We also saw very little response by the intradermal route which has been used classically for immunization with the prototypical replication–competent poxvirus, vaccinia." Whether that response was insufficient to protect the animal against tumor cell challenge is only speculation. Thus, the reference does not provide sufficient evidence to demonstrate the inoperability of a poxvirus vector, much less the inoperability of other viral vectors such as adenovirus.

The *ex vivo* examples of the specification, demonstrate the propensity of adenovirus for dendritic cells. Furthermore, adenoviral vectors have been shown to elicit humoral and cellular immunity, as described in the specification, in various publications. For example, Gilbert *et al.* (*Vaccine* 15;20(7-8):1039-45, 2002) found that recombinant replication-defective adenovirus expressing the CS gene from *Plasmodium berghei* (Ad-PbCS) induced a strong CD8(+) T cell response after intradermal or muscular injection. Therefore, in view of the working examples in the specification using intravenous, subcutaneous or intraperitoneal injection; the insufficiency of the scientific reason for doubting the enablement of the claimed invention and the evidence

provided, Applicants have more than adequately demonstrated the enablement of intradermal administration of an adenovirus in connection with the invention.

Removal of the rejection is thus respectfully requested.

iii.) Claims 1-4, 11-31 and 33-37 are Enabled for Methods Comprising Various Self Gene Products

The Action dated June 26, 2002 concedes that methods for inhibiting tumor growth by intradermal administration of a p53 expression construct is enabled. The Action also rejects claimed methods comprising other tumor suppressor genes. The rejection is based on the general dogma of tumorigenesis in view of Vogelstein *et al.* and Restifo *et al.* The rejection concludes that the specification lacks guidance for the treatment of cells that do not overexpress p53 or do not express p53 at all. The Action provides broad generalities that do not rise to a level sufficient to dispute the examples and guidance provided. The argument provided in the Action does not supply *specific* reasons or evidence as to why the use of other self genes would not have a reasonable expectation of success. The art cited supporting the rejection does not provide any evidence that dispute or call into question the extrapolation of the examples provided in the specification to other self genes, particularly tumor suppressor genes.

The scientific reasoning provided in previous and current Actions is not sufficient to establish a *prima facie* case of lack of enablement pertaining to other self genes. Vogelstein *et al.* and Restifo *et al.* do not provide evidence that rebut the exemplary embodiments and guidance provided in the specification. The specification provides a working example for methods of treatment by expression of a tumor suppressor protein by a dendritic cell, as well as guidance for the identification of other self genes. Applicants note that the dendritic cell is a vehicle for presentation of an epitope and any function of a particular polypeptide is irrelevant.

The examiner is directed to the guidance provided in the specification, at least, on pages 28 to 31, which teaches one of skill in the art how to identify other self genes, including tumor suppressor genes, that are upregulated or have altered expression in cancer cells. This guidance, taken in light of the working examples, teaches one skilled in the art how to identify and use the expression of a self gene by a dendritic cell as a treatment for a cancer involving the over expression or altered expression of a self gene, including a tumor suppressor.

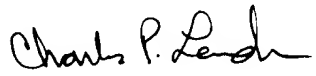
Thus, the heterogeneity of tumor suppressor or oncogene mutations in particular tumors is irrelevant due to the guidance provided in identifying at least one tumor suppressor or oncogene product. Furthermore, the various mechanisms by which tumor cells evade an innate immune response has no bearing on a stimulated immune response as provided in the examples provided in the instant specification.

In view of the foregoing, removal of the rejection is respectfully requested.

E. Conclusion

In light of the preceding amendments and remarks, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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APPENDIX A: VERSION OF CLAIM AMENDMENTS MARKED TO SHOW CHANGES

1. (Amended twice) A method for treating a human subject [with a hyperproliferative] having or suspected of having cancer or pre-cancerous disease comprising the steps of:

(i) identifying a subject [with a hyperproliferative] having or suspected of having cancer or pre-cancerous disease characterized by alteration or increased expression of a self gene product in at least some of the [hyperproliferative] cancer or pre-cancerous cells in said subject; and

(ii) intradermally administering to said subject an expression construct in an adenovirus [viral] particle comprising a self gene under the control of a promoter operable in eukaryotic dendritic cells, wherein the dendritic cells are infected by said construct,

whereby said self gene product is expressed by dendritic cells and presented to immune effector cells, thereby stimulating an anti-self gene product response.

15. (Amended) The method of claim 1[14], wherein said adenovirus[al vector] particle is replication-defective.

28. (Amended) The method of claim 26, wherein the injection is performed local to a cancer, a pre-cancer[hyperproliferative] or a tumor site.

29. (Amended) The method of claim 26, wherein the injection is performed regional to a cancer, a pre-cancer[hyperproliferative] or a tumor site.

30. (Amended) The method of claim 26, wherein the injection is performed distal to a cancer, a pre-cancer[hyperproliferative] or a tumor site.